Biology 76/176: Advanced Genetics

Fall 2018
Lecture: M, W, F 11:30 AM-12:35 PM; x-hour Tu 12:00-12:50

C. Robertson McClung
323 Life Sciences Complex

Office Hours: Monday-Friday 2:00-4:00 PM
or by appointment

Course Content

This course provides in-depth coverage of the analysis of gene inheritance and function. Biology 76 will build on material covered in Biology 13 and Biology 45, emphasizing the use of model organisms to obtain information relevant to important problems.

Text

There will be no text, but your text from earlier Genetics classes (e.g., Russell iGenetics 3e) might prove useful as a resource.

Evaluation

Your grade will be based on four written assignments—study guides based on the analysis of a paper from the primary literature. The first three will be worth 20% each and the final assignment will be worth 30%. In addition, 10% of your grade will be based on class participation. This includes attendance (to paraphrase 80% of success is showing up) as well as your willingness and ability to contribute meaningfully to class discussion. Examples of this would include your providing a clear explanation of a figure from the assigned reading to the class or asking thought-provoking questions about the topics under consideration. The first three assignments that will be discussed in class will be due at **the beginning** of the class in which they are to be discussed. The method of submission is electronic—email me your file before class begins. The fourth assignment will be due at 1130 AM on Nov 20 (the last day of final exams). **Late assignments will be penalized** 25% of the earned grade per day or part thereof unless a prior arrangement is finalized **in writing**.

Please note that the Discussions will be held Fridays in the regular class time (11:30 AM-12:35 PM).

Disability Notice

Students with disabilities who may need disability-related academic adjustments and services for this course are encouraged to see me privately as early in the term as possible. Students requiring disability-related academic adjustments and services must consult the Student Accessibility Services office (205 Collis Student Center, 646-9900, Student.Accessibility.Services@Dartmouth.edu). Once SAS has authorized services, students must show the originally signed SAS Services and Consent Form and/or a letter on SAS letterhead to their professor. As a first step, if students have questions about whether they qualify to receive academic adjustments and services, they should contact the SAS office. All inquiries

and discussions will remain confidential.

Your Health

I recognize that the academic environment at Dartmouth is challenging, that our terms are intensive, and that classes are not the only demanding part of your life. There are a number of resources available to you on campus to support your wellness, including: your undergraduate dean (http://www.dartmouth.edu/~upperde/), Counseling and Human Development (http://www.dartmouth.edu/~chd/), and the Student Wellness Center (http://www.dartmouth.edu/~healthed/). I encourage you to use these resources as you deem appropriate and to come to talk with me if you have any concerns. It is important to take care of yourself throughout the term.

Religious Holidays

Some students may wish to take part in religious observances that occur during this academic term. If you have a religious observance that conflicts with your participation in this course, please meet with me as soon as possible to discuss appropriate accommodations.

The Honor Principle

Academic honesty is essential. The following is quoted directly from the Dartmouth College Student Handbook: "Fundamental to the principle of independent learning are the requirements of honesty and integrity in the performance of academic assignments, both in and out of the classroom. Dartmouth operates on the principle of academic honor, without proctoring of examinations. Any student who submits work which is not his or her own, or commits other acts of academic dishonesty, violates the purposes of the college and is subject to disciplinary actions, up to and including suspension or separation." The complete text of the Academic Honor Principle is in the Student Handbook. Please read it carefully. Graduate students should consult the Graduate Student Handbook, with particular emphasis on The Honor Principle and Code of Conduct. Any violations of the Honor Principle within the context of Biology 76/176 will be referred to the Committee on Standards or to the Dean of Graduate Studies, respectively.

Awareness of the Academic Honor Principle is not intended to inhibit discussion of the class material among the students. Indeed, such discussion is worthwhile and constitutes a valuable component of the learning process and is encouraged on the first four study guide assignments. However, the study guides must be written independently. Two assignments by two individuals who had discussed the assignment almost certainly will reflect ideas developed by the two together, but each student must phrase their assignment in their own words and acknowledge the "helpful discussions" with their collaborators. Do not share computer files! To do so constitutes plagiarism. The **Fourth Assignment** is in open book format (all written resources are permitted) but is to be **done entirely on one's own (no collaboration**).

Schedule (subject to change)

	Topic	Reading
1. Sep 12	Introduction/Genetics in the Genomics Age	(Mushegian and Koonin, 1996; Glass et al., 2006; Hutchison III et al., 2016)
Section 1, Forward Genetics		
2. Sep 14	Mutation Rates & Mutant Selections	(Haag-Liautard et al., 2007; Lang and Murray, 2008; Ossowski et al., 2010; Winston and Koshland, 2016)
3. Sep 17	Mutant Screens: Heterochrony in Worms	(Ambros and Horvitz, 1984)
4. Sep 19	Complementation, Suppression, Enhancement	(Ambros and Horvitz, 1987)
5. Sep 21	Study Guide Warm-up: The molecular discovery of microRNAs	(Lee et al., 1993; Reinhart et al., 2000)
6. Sep 24	Epistasis	(Ambros, 1989; Avery and Wasserman, 1992)
7. Sep 26	Sex determination in Drosophila I	(Keyes et al.; Penalva and Sánchez, 2003)
8. Sep 28	Study Guide 1 (20%)	(Ustianenko et al., 2018)
9. Oct 1	Sex determination in Drosophila II	(Erickson and Quintero, 2007)
10. Oct 3	Cystic Fibrosis	(Fanen et al., 2014; Cutting, 2015)
11. Oct 5	Genetic Modifiers in Cystic Fibrosis	(Kiesewetter et al., 1993; Drumm et al., 2005)
12. Oct 8	Anteroposterior polarity in Drosophila I	(Frohnhöfer and Nüsslein-Vollhard, 1986; Nusslein-Volhard et al., 1987)
13. Oct 10	Anteroposterior polarity in Drosophila II	(Berleth et al., 1988; Driever and Nüsslein-Volhard, 1988; Spirov et al., 2009)
14. Oct 12	RNAi in *C. elegans* and plants	(Fire et al., 1998; Hamilton and Baulcombe, 1999)
Section 2, Reverse Genetics		
15. Oct 15	Anteroposterior polarity in *C. elegans*	(Griffin et al., 2011)
16. Oct 17	Screens in human tissue culture	(Zhang et al., 2009; Partch et al., 2014)

17. Oct 19	Study Guide 2 (20%)	(Farboud et al., 2013)
18. Oct 22	Gene replacement in Yeast	(Boeke et al., 1985; Winzeler and al., 1999; Giaever et al., 2002)
19. Oct 24	Transgenic Mice (knockouts/knockins) I	(Mansour et al., 1988; Garcia-Cao et al., 2012)
20. Oct 26	Transgenic Mice (knockouts/knockins) II	(Mansour et al., 1988; Garcia-Cao et al., 2012)
21. Oct 29	RNAi Screens in mice	(Beronja et al., 2013)
22. Oct 31	CRISPR-mediated genome editing	(Gilbert et al., 2013; Gilbert et al., 2014)
23. Nov 2	Chemical Genomics	(Baragana, 2015)

Section 3, Quantitative Genetics

24. Nov 5	Quantitative Trait Loci	(Barton and Keightley, 2012)
25. Nov 7	Genome-Wide Association Studies	(Consortium, 2007; Atwell et al., 2010; Chao et al., 2012)
26. Nov 9	Study Guide 3 (20%)	(Norris et al., 2017)
27. Nov 12	Complex Traits: a tomato example	(Müller et al., 2016; Müller et al., 2018)
29. Nov 20 (no meeting, but assignment due by 1130 AM)	Study Guide 4 (30%)	(Lu et al., 2017)

Reading List

Ambros, V. (1989). A hierarchy of regulatory genes controls a larva-to-adult developmental switch in C. elegans. Cell **57:** 49-57.

Ambros, V., and Horvitz, H.R. (1984). Heterochronic mutants of the nematode *Caenorhabditis elegans*. Science **226:** 409-416.

Ambros, V., and Horvitz, H.R. (1987). The *lin-14* locus of *Caenorhabditis elegans* controls the time of expression of specific postembryonic developmental events. American Zoologist **1:** 398-414.

Atwell, S., Huang, Y.S., Vilhjálmsson, B.J., Willems, G., Horton, M., Li , Y., Meng, D., Platt, A., Tarone, A.M., Hu, T.T., Jiang, R., Muliyati, N.W., Zhang, X., Amer, M.A., Baxter, I., Brachi, B., Chory, J., Dean, C., Debieu, M., de Meaux, J., Ecker, J.R., Faure, N., Kniskern, J.M., Jones, J.D., Michael, T., Nemri, A., Roux, F., Salt, D.E., Tang, C., Todesco, M., Traw, M.B., Weigel, D., Marjoram, P., Borevitz , J.O., Bergelson, J., and Nordborg, M. (2010). Genome-wide association study of 107 phenotypes in *Arabidopsis thaliana* inbred lines. Nature **465:** 627-631.

Avery, L., and Wasserman, S. (1992). Ordering gene function: the interpretation of epistasis in regulatory hierarchy. Trends Genet. **8:** 312-316.

Baragana, B., et al. (2015). A novel multiple-stage antimalarial agent that inhibits protein synthesis. Nature **522:** 315-320.

Barton, N.H., and Keightley, P.D. (2012). Understanding quantitative genetic variation. Nature Rev. Genetics **3:** 11-21.

Berleth, T., Burri, M., Thoma, G., Bopp, D., Richstein, S., Frigerio, G., Noll, M., and Nusslein-Volhard, C. (1988). The role of localization of bicoid RNA in organizing the anterior pattern of the *Drosophila* embryo. EMBO J. **7:** 1749-1756.

Beronja, S., Janki, P., Heller, E., Lien, W.-H., Keyes, B.E., Oshimori, N., and Fuchs, E. (2013). RNAi screens in mice identify physiological regulators of oncogenic growth. Nature **501**.

Boeke, J.D., Garfinkel, D.J., Styles, C.A., and Fink, G.R. (1985). Ty elements transpose through an RNA intermediate. Cell **40:** 491-500.

Chao, D.-Y., Silva, A., Baxter, I., Huang, Y.S., Nordborg, M., Danku, J., Lahner, B., Yakubova, E., and Salt, D.E. (2012). Genome-wide association studies Identify heavy metal ATPase3 as the Primary determinant of natural variation in leaf cadmium in *Arabidopsis thaliana*. PLoS Genet. **8:** e1002923.

Consortium, T.W.T.C.C. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature **447:** 661-678.

Cutting, G.R. (2015). Cystic fibrosis genetics: from molecular understanding to clinical application. Nature Rev. Genetics **16:** 45-56.

Driever, W., and Nüsslein-Volhard, C. (1988). A gradient of *bicoid* protein in Drosophila embryos. Cell **54:** 83-93.

Drumm, M.L., Konstan, M.W., Schluchter, M.D., Handler, A., Pace, R., Zou, F., Zariwala, M., Fargo, D., Xu, A., Darrah, R.J., Dorfman, R., Sandford, A.J., Corey, M., Zielenski, J., Durie, P., Goddard, K., Yankaskas, J.R., Wright, F.A., and Knowles, M.R. (2005). Genetic modifiers of lung disease in cystic fibrosis. New Engl. J. Med. **353:** 1443-1453.

Erickson, J.W., and Quintero, J.J. (2007). Indirect effects of ploidy suggest X chromosome dose, not the X:A ratio, signals sex in *Drosophila* PLoS Biol. **5:** e332.

Fanen, P., Wohlhuter-Haddad, A., and Hinzpetera, A. (2014). Genetics of cystic fibrosis: CFTR mutation classifications towardgenotype-based CF therapies. Intl. J. Biochem. Cell Biol. **52:** 94-102.

Farboud, B., Nix, P., Jow, M.M., Gladden, J.M., and Meyer, B.J. (2013). Molecular antagonism between X-chromosome and autosome signals determines nematode sex. American Zoologist **27:** 1159-1178.

Fire, A., Xu, S.-Q., Montgomery, M.K., Kostas, S.A., Driver, S.E., and Mello, C.C. (1998). Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature **391:** 806-811.

Frohnhöfer, H.G., and Nüsslein-Vollhard, C. (1986). Organization of the anterior pattern in the *Drosophila* embryo by the nmaternal gene *bicoid*. Nature **324:** 120-125.

Garcia-Cao, I., Song, Min S., Hobbs, Robin M., Laurent, G., Giorgi, C., de Boer, Vincent C.J., Anastasiou, D., Ito, K., Sasaki, Atsuo T., Rameh, L., Carracedo, A., Vander Heiden, Matthew G., Cantley, Lewis C., Pinton, P., Haigis, Marcia C., and Pandolfi, Pier P. (2012). Systemic Elevation of PTEN Induces a Tumor-Suppressive Metabolic State. Cell **149:** 49-62.

Giaever, G., Chu, A.M., Ni, L., Connelly, C., Riles, L., Veronneau, S., Dow, S., Lucau-Danila, A., Anderson, K., Andre, B., Arkin, A.P., Astromoff, A., El Bakkoury, M., Bangham, R., Benito, R., Brachat, S., Campanaro, S., Curtiss, M., Davis, K., Deutschbauer, A., Entian, K.D., Flaherty, P., Foury, F., Garfinkel, D.J., Gerstein, M., Gotte, D., Guldener, U., Hegemann, J.H., Hempel, S., Herman, Z., Jaramillo, D.F., Kelly, D.E., Kelly, S.L., Kotter, P., LaBonte, D., Lamb, D.C., Lan, N., Liang, H., Liao, H., Liu, L., Luo, C.Y., Lussier, M., Mao, R., Menard, P., Ooi, S.L., Revuelta, J.L., Roberts, C.J., Rose, M., Ross-Macdonald, P., Scherens, B., Schimmack, G., Shafer, B., Shoemaker, D.D., Sookhai-Mahadeo, S., Storms, R.K., Strathern, J.N., Valle, G., Voet, M., Volckaert, G., Wang, C.Y., Ward, T.R., Wilhelmy, J., Winzeler, E.A., Yang, Y.H., Yen, G., Youngman, E., Yu, K.X., Bussey, H., Boeke, J.D., Snyder, M., Philippsen, P., Davis, R.W., and Johnston, M. (2002). Functional profiling of the *Saccharomyces cerevisiae* genome. Nature **418:** 387-391.

Gilbert, L.A., Larson, M.H., Morsut, L., Liu, Z., Brar, G.A., Torres, S.E., Stern-Ginossar, N., Brandman, O., Whitehead, E.H., Doudna, J.A., Lim, W.A., Weissman, J.S., and Qi, L.S. (2013). CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. Cell **154:** 442-451.

Gilbert, Luke A., Horlbeck, Max A., Adamson, B., Villalta, Jacqueline E., Chen, Y., Whitehead, Evan H., Guimaraes, C., Panning, B., Ploegh, Hidde L., Bassik, Michael C., Qi, Lei S., Kampmann, M., and Weissman, Jonathan S. (2014). Genome-scale CRISPR-mediated control of gene repression and activation. Cell **159:** 647-661.

Glass, J.I., Assad-Garcia, N., Alperovich, N., Yooseph, S., Lewis, M.R., Maruf, M., Hutchison III, C.A., Smith, H.O., and Venter, J.C. (2006). Essential genes of a minimal bacterium. Proc. Natl. Acad. Sci. USA **103:** 425-430.

Griffin, Erik E., Odde, David J., and Seydoux, G. (2011). Regulation of the MEX-5 gradient by a spatially segregated kinase/phosphatase cycle. Cell **146:** 955-968.

Haag-Liautard, C., Dorris, M., Maside, X.M., Steven , Halligan, D.L., Charlesworth, B., and Keightley, P.D. (2007). Direct estimation of per nucleotide and genomic deleterious mutation rates in *Drosophila*. Nature **445:** 82-85.

Hamilton, A.J., and Baulcombe, D.C. (1999). A species of small antisense RNA in posttranscriptional gene silencing in plants. Science **286:** 950-952.

Hutchison III, C.A., Chuang, R.-Y., Noskov, V.N., Assad-Garcia, N., Deerinck, T.J., Ellisman, M.H., Gill, J., Kannan, K., Karas, B.J., Ma, L., Pelletier, J.F., Qi, Z.-Q., Richter, R.A., Strychalski, E.A., Sun, L., Suzuki, Y., Tsvetanova, B., Wise, K.S., Smith, H.O., Glass, J.I., Merryman, C., Gibson, D.G., and Venter, J.C. (2016). Design and synthesis of a minimal bacterial genome. Science **351:** 1414.

Keyes, L.N., Cline, T.W., and Schedl, P. (1992). The primary sex determination signal of Drosophila acts at the level of transcription. Cell **68:** 933-943.

Kiesewetter, S., Macek, M., Davis, C., Curristin, S.M., Chu, C.-S., Graham, C., Shrimpton, A.E., Cashman, S.M., Tsui, L.-C., Mickle, J., Amos, J., Highsmith, W.E., Shuber, A., Witt, D.R., Crystal, R.G., and Cutting, G.R. (1993). A mutation in CFTR produces different phenotypes depending on chromosomal background. Nature Genet. **5:** 274-278.

Lang, G.I., and Murray, A.W. (2008). Estimating the per-base-pair mutation rate in the yeast *Saccharomyces cerevisiae*. Genetics **178:** 67-82.

Lee, R.C., Feinbaum, R.L., and Ambros, V. (1993). The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. Cell **75:** 843-854.

Lu, S., Zhao, X., Hu, Y., Liu, S., Nan, H., Li, X., Fang, C., Cao, D., Shi, X., Kong, L., Su, T., Zhang, F., Li, S., Wang, Z., Yuan, X., Cober, E.R., Weller, J.L., Liu, B., Hou, X., Tian, Z., and Kong, F. (2017). Natural variation at the soybean *J* locus improves adaptation to the tropics and enhances yield. Nat. Genet. **49:** 773-779.

Mansour, S.L., Thomas, K.R., and Capecchi, M.R. (1988). Disruption of the proto-oncogene *int-2* in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes. Nature **336** 348-352.

Müller, N.A., Zhang, L., Koornneef, M., and Jiménez-Gómez, J.M. (2018). Mutations in *EID1* and *LNK2* caused light-conditional clock deceleration during tomato domestication. Proc. Natl. Acad. Sci. USA **115:** 7135-7140.

Müller, N.A., Wijnen, C., Srinivasan, A., Ryngajllo, M., Ofner, I., Lin, T., Ranjan, A., West, D., Maloof, J.N., Sinha, N.R., Huang, S., Zamir, D., and Jiménez-Gómez, J.M. (2016). Domestication selected for deceleration of the circadian clock in cultivated tomato. Nat. Genet. **48:** 89-93.

Mushegian, A.R., and Koonin, E.V. (1996). A minimal gene set for cellular life derived by comparison of complete bacterial genomes. Proc. Natl. Acad. Sci. USA **93:** 10268-10273.

Norris, A.D., Gracida, X., and Calarco, J.A. (2017). CRISPR-mediated genetic interactionprofiling identifies RNA binding proteinscontrolling metazoan fitness. eLIFE **6:** e28129.

Nusslein-Volhard, C., Frohnhofer, H.G., and Lehmann, R. (1987). Determination of anteroposterior polarity in *Drosophila*. Science **238:** 1675-1681.

Ossowski, S., Schneeberger, K., Lucas-Lledó, J.I., Warthmann, N., Clark, R.M., Shaw, R.G., Weigel, D., and Lynch, M. (2010). The rate and molecular spectrum of spontaneous mutations in *Arabidopsis thaliana*. Science **327:** 92-94.

Partch, C.L., Green, C.B., and Takahashi, J.S. (2014). Molecular architecture of the mammalian circadian clock. Trends Cell Biol. **24:** 90-99.

Penalva, L.O.F., and Sánchez, L. (2003). RNA binding protein Sex-Lethal (Sxl) and control of Drosophila sex determination and dosage compensation. Microbiol. Mol. Biol. Rev. **67:** 343-359.

Reinhart, B.J., Slack, F.J., Basson, M., Pasquinelli, A.E., Bettinger, A.E., Rougvie, A.E., Horvitz, H.R., and Ruvkun, G. (2000). The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. Nature **403:** 901-906.

Spirov, A., Fahmy, K., Schneider, M., Frei, E., Noll, M., and Baumgartner, S. (2009). Formation of the bicoid morphogen gradient: an mRNA gradient dictates the protein gradient. Development **136:** 605-614.

Ustianenko, D., Chiu, H.-S., Treiber, T., Weyn-Vanhentenryck, S.M., Treiber, N., Meister, G., Sumazin, P., and Zhang, C. (2018). LIN28 selectively modulates a subclass of Let-7 microRNAs. Mol. Cell **71:** 271–283.

Winston, F., and Koshland, D. (2016). Back to the future: Mutant hunts are still the way to go. Genetics **203:** 1007-1010.

Winzeler, E.A., et al., (1999). Functional characterization of the *S. cerevisiae* genome by gene deletion and parallel analysis. Science **285:** 901-906.

Zhang, E.E., Liu, A.C., Hirota, T., Miraglia, L.J., Welch, G., Pongsawakul, P.Y., Liu, X., Atwood, A., Huss III, J.W., Janes, J., Su, A.I., Hogenesch, J.B., and Kay, S.A. (2009). A genome-wide RNAi screen for modifiers of the circadian clock in human cells. . Cell **139:** 199-210